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ORIGINAL PAPER

Ex-PRESS outcomes using mitomycin-C, Ologen alone, Ologen with 5-fluorouracil

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Abstract To compare the complication rate and effectiveness of mitomycin C (MMC), Ologen alone, and Ologen with 5-fluorouracil (5-FU) as adjunctives with Ex-PRESS mini shunt for medically uncontrolled glaucoma. Retrospective comparative study of 59 Ex-PRESS mini shunt trabeculectomy operations coupled with Ologen implantation alone, transient MMC application or Ologen implantation with 5-FU as adjunctive treatment. Eight eyes (7 patients) received Ologen alone, 37 eyes (34 patients) received MMC, and 14 eyes (14 patients) received Ologen with 5-FU as adjunctive therapy. Baseline characteristics, adjunctive used during operation, along with outcomes including intraocular pressure (IOP), number of anti-hypertensive drops, visual acuity, and complications were documented and compared. The primary outcome was IOP at 12 months. Variables were compared with $r \times c$ Fisher tests. The Ologen only group had a significantly higher IOP at 12 months (20.5 ± 10.23 mmHg) compared with Ologen combined with 5-FU (12.2 ± 1.47 mmHg) or MMC (13.8 ± 4.37 mmHg) ($p = 0.015$, linear mixed model). The Ologen only cohort also had a higher re-operation rate ($p = 0.01$, Fisher's Exact Test) and higher rate of bleb leak ($p = 0.02$, Fisher's Exact Test). Visual acuity was similar among all three groups. 5-FU with Ologen is as effective as MMC in maintaining IOP following Ex-PRESS shunt surgery at 1 year. However, Ologen alone may not be as effective as the other two adjunctive agents.

Keywords Glaucoma surgery · Ologen · Ex-PRESS shunt

Introduction

The Ex-PRESS mini shunt (Alcon Laboratories, Fort Worth, TX, USA) is a non-valved, stainless steel

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device that can offer an alternative to standard trabeculectomy. The primary advantages of the Ex-PRESS shunt are the ease with which it is inserted and the decreased need for a peripheral iridectomy. The Ex-PRESS implant has been shown to have similar intraocular pressure (IOP)-lowering effect as standard trabeculectomy with a lower rate of early post-operative hypotony [1]. Adjunctive use of agents such as transient application of mitomycin C (MMC) and 5-fluorouracil (5-FU) has been shown to significantly improve long-term success for standard trabeculectomy and decreases dependence on anti-glaucoma medications [2]. MMC and 5-FU reduce scar formation at the level of the episcleral space, enhance aqueous flow, and lower the rate of surgical failure [3]. However, depending on dosage and application method, these agents can be associated with severe post-operative complications including hypotony, late leakage, and endophthalmitis [3–5].

The Ologen collagen matrix is a biodegradable porcine-derived collagen–glycosaminoglycan matrix that has been shown to decrease early post-operative scarring in animal models [6, 7]. When Ologen is placed directly over the scleral flap, fibroblasts migrate into the pores. The fibroblasts then secrete a loose matrix in a random fashion rather than an organized way, reducing scar formation. The Ologen has been reported to be reabsorbed within 6 months [8]. After the Ologen has been reabsorbed, the result, theoretically, should be a loosely structured but not cystic bleb.

The effectiveness of Ologen in clinical practice remains controversial with some studies showing equivalent results to MMC [8–10], others showing higher rates of complications [11], and others was showing lower pressure reductions than MMC [12–14]. A recent meta-analysis showed greater IOP reduction with MMC that was significant at 12 months follow-up, but noted the persistent scarcity of comparative studies with Ologen [15]. In addition, there is no study to compare the effectiveness of Ologen when it is combined with less potent but safer anti-fibrotic agent, such as 5-FU.

We retrospectively compared the effectiveness and complication rates of Ex-PRESS shunt in patients with medically uncontrolled glaucoma coupled with one of three different adjunctive techniques: transient MMC application, Ologen implantation with 5-FU, or Ologen implantation alone.

Materials and methods

This was a two-center retrospective, comparative study including all uncontrolled glaucoma patients from January 2009 through December 2011. The study was approved by the Institutional Review Board. We reviewed the records of all uncontrolled glaucoma patients who underwent Ex-PRESS shunt placement with the addition of an adjunctive therapy including Ologen only, Ologen with 5-FU, and MMC without Ologen at two hospitals associated with one residency program. Utilization of Ologen alone was discontinued when poor outcomes were noted, thus limiting the number of patients in this group.

All patients needing an anterior filtering surgery due to uncontrolled glaucoma despite maximally tolerated medications were included. Pre-operative data assessed included patient age, sex, glaucoma diagnosis, and glaucoma medications. Before the surgical intervention, all patients underwent a baseline examination. This included measurement of best-corrected visual acuity (BCVA), visual field examination with 30-2 on a Humphrey field analyzer, and Goldman applanation tonometery.

The surgeries were undertaken in the following manner: a superior conjunctival peritomy was performed, and conjunctiva as well as Tenon's layer was undermined posteriorly for 6 or 7 mm. A half-thickness incision was made 3–4 mm posterior to the limbus into sclera. A scleral tunnel was created into clear cornea, and the edges were extended anteriorly to cut a scleral flap. In the MMC group, two sponges soaked in 0.5 mg/ml of MMC were placed into the sub-Tenons space for 3–4 min. The sponges were then removed, and the area was irrigated copiously with balanced salt solution. A temporal paracentesis was created. A 26-gauge needle was used to create a track into the anterior chamber underneath the scleral flap, and a P50 Ex-PRESS shunt was injected through the pre-incised track. Aqueous flow was confirmed. The scleral flap was closed until only a small amount of leakage was noted from the posterior portion of the scleral flap. In the Ologen alone group, a 2 mm by 6 mm section Ologen was inserted unto the sub-Tenon space posterior to the scleral flap prior to conjunctival closure. In the Ologen with 5-FU group, a 2 mm by 6 mm of Ologen implant soaked in 5-FU (50 mg/ml) was then placed under the conjunctiva posterior to the scleral flap. The conjunctiva was closed

with either a running 8-0 polygalactin suture to a small remaining anterior flap of conjunctiva or with two interrupted 8-0 polygalactin wing sutures accompanied by a central limbal 10-0 nylon mattress suture from conjunctiva to cornea.

Data were collected from the 1 month, 3 months, 6 months, and 1 year post-operative examinations, but complications were recorded at all the post-operative visits. Information abstracted included BCVA, Goldman applanation tonometry, and number of post-operative eye drop medications. Early complications were defined as those occurring at or prior to 1 month, and late complications were defined as those occurring 1 month after the placement of the Ex-PRESS shunt. Early complications included choroidal effusions, shallow or flat chamber, wound leak, hyphema, aqueous misdirection, suprachoroidal hemorrhage, and vitreous hemorrhage. Late complications included persistent choroidal effusions, hypotony lasting for 3 or more months with an IOP of 5 mmHg or less, bleb leak, endophthalmitis, chronic or recurrent uveitis, and retinal detachment. Additional complications monitored included number of re-operations and number of laser suture lysis.

The primary outcome was IOP at 12 months. We also performed a loss to follow-up analysis comparing baseline IOP and number of glaucoma medication in those following up to care against those lost to follow-up using heteroscedastic t testing. Categorical variables were compared with $r \times c$ Fisher tests. Continuous variables in which there were multiple measurements over time were compared using linear mixed effects regression, while continuous variables with a single recorded value per patient were analyzed with one-way ANOVA (ordinary least squares). Count variables were compared using the Kruskal–Wallis rank sum test because substantial departures from normality were expected. All analyses were conducted in R (v. 2.14 for MacIntosh, R Foundation for Statistical Computing, Vienna, Austria).

Table 1 Baseline characteristics

	Ologen only	Ologen + 5-FU	Mitomycin C	p value
Total procedures	8	14	37	–
Age	69.2 (±7.4)	74.8 (±11.2)	72.6 (±11.5)	0.52
% Male	7 (88 %)	11 (79 %)	31 (84 %)	0.88
POAG	3 (38 %)	10 (71 %)	28 (76 %)	0.12
MMG	1 (13 %)	1 (7 %)	2 (5 %)	
CNAG	1 (13 %)	1 (7 %)	0 (0 %)	
PXG	1 (13 %)	2 (14 %)	5 (14 %)	
NTG	2 (13 %)	0 (0 %)	2 (5 %)	
% Right eye	2 (25 %)	7 (50 %)	15 (41 %)	0.59
Pre-op IOP	25.9 (±14.4)	24.4 (±7.5)	23.8 (±9.0)	0.82
Pre-op BCVA	0.68 (±0.69)	0.40 (±0.57)	0.41 (±0.56)	0.45
Pre-op # gtts	3.25 (±0.46)	2.93 (±1.07)	3.22 (±0.89)	0.631
Pseudophakic	3 (38 %)	7(50 %)	12 (33 %)	0.50
Pre-op HVF MD	−16.0 (±9.0)	−12.9 (±11.7)	−15.7 (±7.8)	0.633
Pre-op HVF PSD	9.0 (±2.7)	5.9 (±3.4)	7.8 (±3.6)	0.117
Combined with phaco	2 (25 %)	2 (14 %)	7 (19 %)	0.79
Diabetes mellitus	2 (25 %)	2 (14 %)	11 (30 %)	0.61
Hypertension	1 (13 %)	5 (36 %)	27 (73 %)	**0.002**

Bold signifies significant to a $P < 0.05$ level.

Baseline characteristics of population in each treatment branch. Continuous variables are given with standard deviation. Statistical analysis performed with one-way ANOVA for linear variables and $r \times c$ Fisher test for categorical variables

POAG primary open angle glaucoma, *MMG* mixed-mechanism glaucoma, *CNAG* chronic narrow angle glaucoma, *PXG* pseudoexfoliative glaucoma, *NTG* normal tension glaucoma, *BCVA* best-corrected visual acuity (measured in logMar), *# gtts* number of glaucoma medications, *HVF* Humphrey visual field, *MD* mean deviation, *PSD* pattern standard deviation

Table 2 IOP before surgery and at follow-up

	Ologen only		Ologen + 5-F		Mitomycin C		*p* value
	N	IOP	*N*	IOP	*N*	IOP	
Pre-operative	8	25.88	14	24.36	37	23.84	0.8183
1 month	8	18.63	12	15.67	36	12.31	**0.033**
3 months	8	13.44	13	13.77	34	13.62	0.996
6 months	8	21	11	13.41	28	14	0.11
12 months	8	20.50	6	12.17	19	13.84	**0.015**

Bold signifies significant to a $P < 0.05$ level.

Measurements of intra-ocular pressure before and after glaucoma surgery using either Ologen only, Ologen and 5-FC, or MMC. Ologen only group has a significantly higher IOP at 12 months ($p = 0.015$). Statistical analysis performed with linear mixed effects regression

Results

There were 8 eyes (7 patients) in the Ologen alone group, 37 eyes (34 patients) in the MMC group, and 14 eyes (14 patients) in the Ologen with 5-FU group. Table 1 shows the pre-operative characteristics of the three groups. Among the three groups, there was no significant difference in pre-operative IOP, number of ophthalmic medications, gender, age, pre-operative BCVA, pre-operative Humphrey visual field mean deviation, and pre-operative Humphrey visual field pattern standard deviation (Table 1).

IOP was significantly higher at 1 year in the Ologen only group compared against the Ologen with 5-FU group and the MMC group. At 12 months after surgery, the Ologen only group had a significantly higher average IOP of 20.5 mmHg compared with 13.84 mmHg in the MMC cohort and 12.17 mmHg in the Ologen with 5-FU cohort ($p = 0.015$) as seen in Table 2 and Fig. 1.

We compared the baseline IOP and number of glaucoma medications of those completing the full 1 year follow-up with those not following up in each cohort at 1, 3, 6, and 12 months. The only statistically significant difference was seen at 6 months in the MMC group where those following up to care tended to have higher baseline IOP and fewer baseline glaucoma medications than those not following up with respective values of 25.4 versus 18.9. ($p = 0.001$) and 3.07 versus 3.67 ($p = 0.02$). Additionally, BCVA and number of eye drop medications were not statistically different between the three groups at 3, 6, or 12 months follow-up ($p > 0.10$).

Tables 3 and 4 summarize the early and late complications observed in each group. Early complications

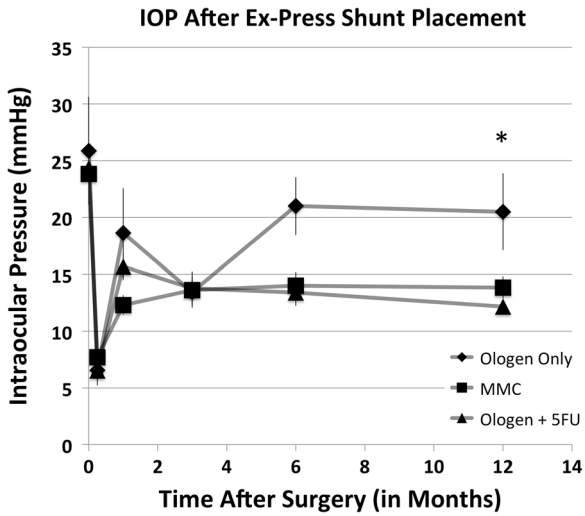

Fig. 1 Average IOP at time of surgery (time = 0) and at follow-up. Ologen only, Mitomycin C, and Ologen with 5-FU groups depicted by *diamonds*, *squares*, and *triangles*, respectively. *Error bars* represent the standard error of the mean. The *asterisk* marks the significant difference between the Ologen only group compared with the Ologen with 5-FU and MMC groups at 12 months ($p = 0.015$, linear mixed modeling)

including choroidal detachment, shallow or flat chamber, wound leak, and hyphema were seen in all the groups, and there were no statistically significant differences between the groups. There was one episode of suprachoroidal hemorrhage in the 5-FU group and one episode of vitreous hemorrhage in the MMC group. Delayed complications seen after 1 month at similar rates between all three groups included choroidal detachment and hypotony with an IOP less than 5 mmHg for over 3 months. Bleb leak occurred in 2 eyes (25 %) in the Ologen alone group ($p = 0.02$). There was only one case

Table 3 Complications at less than 1 month post-operative

	Ologen only	Ologen + 5-FU	Mitomycin C	*p* value
Choroidals	4 (50 %)	5 (36 %)	9 (24 %)	0.24
Shallow or flat chamber	4 (50 %)	5 (36 %)	9 (24 %)	0.24
Wound leak	2 (25 %)	5 (36 %)	10 (27 %)	0.7
Hyphema	3 (38 %)	4 (29 %)	3 (8 %)	0.051
Aqueous misdirection	0 (0 %)	0 (0 %)	0 (0 %)	–
Suprachoroidal hemorrhage	0 (0 %)	1 (7 %)	0 (0 %)	0.36
Vitreous hemorrhage	0 (0 %)	0 (0 %)	0 (0 %)	–

Comparison of early complications by surgical group at less than 1-month. Statistical analysis performed with $r \times c$ Fisher Test

Table 4 Delayed complications over 1 month post-operative

	Ologen only	Ologen + 5-FU	Mitomycin C	*p* value
Choroidals	1 (13 %)	2 (14 %)	2 (5 %)	0.3
Hypotony	1 (13 %)	1 (7 %)	2 (5 %)	0.77
Bleb leak	2 (25 %)	0 (0 %)	0 (0 %)	0.02
Endophthalmitis/blebitis	0 (0 %)	0 (0 %)	1 (3 %)	1
Chronic or recurrent iritis	0 (0 %)	0 (0 %)	0 (0 %)	–
Retinal detachment	0 (0 %)	0 (0 %)	0 (0 %)	–
Number of re-operations	3	1	1	**0.01**
Number of laser suture lysis	3	0	19	0.06

Comparison of late complications by surgical group after 1-month. Ologen only had a significantly higher rate of re-operations and bleb leak. Statistical analysis performed with $r \times c$ Fisher Test for categorical variables and Kruskal–Wallis rank sum test for number of re-operations and laser suture lysis

of endophthalmitis, which occurred in the MMC group. Three eyes (37.5 %) in the Ologen alone group required re-operations. Nineteen eyes (51.4 %) in the MMC group required laser suture lysis, while three eyes in the Ologen alone group (37.5 %) required laser suture lysis, and no eyes in the 5-FU group required it ($p = 0.06$).

Discussion

Our study reports of results with the Ex-PRESS shunt in conjunction with commonly used intraoperative adjunctives with intermediate follow-up at 1 year. This study suggests that Ologen alone may not be successful in maintaining IOP given that IOP was significantly higher at 12 months in the Ologen group compared to the 5-FU and MMC cohorts. This is in spite of a higher baseline IOP in the MMC cohort that might be expected to artificially inflate the IOP of the MMC cohort at 12 months. In fact, the use of Ologen alone was stopped during the study due to consistently suboptimal post-operative IOP control and a higher rate of re-operations. This ethical consideration led to a small sample size in the Ologen only group.

The suboptimal performance of Ologen alone compared with MMC or Ologen with 5-FU is consistent with previous reports showing patients who receive MMC rather than Ologen have significantly lower IOP at 12 months [12–14]. This finding was also reinforced recently in a meta-analysis showing that patients undergoing trabeculectomy with MMC rather than Ologen experienced on average 1.94 mm Hg greater reduction in IOP, and that this difference was statistically significant [15]. Although there have been numerous studies that fail to show a difference, these studies have generally not been formally designed as non-inferiority trials and may have failed to show a difference due to lack of power [8–10].

The failure of Ologen alone may be secondary to its interference with posterior flow, which is important in the prevention of episcleral scar formation, and counter-balancing its theoretical benefit of prevention

of scar formation. Additionally, the Ologen implant decreases the access to scleral sutures and makes laser suture lysis technically more difficult. Finally, it appears that the Ologen implant does not always dissolve by 180 days as suggested by early animal studies but is still present in several cases even at 1 year [11]. Eventually, scar tissue is formed around the Ologen implant and this is positioned posterior to the scleral flap, preventing posterior aqueous flow which may account for the observed increased IOP.

MMC application to the surgical site is more effective at maintaining a lowered IOP than intraoperative 5-FU in trabeculectomy [4]. However, 5-FU is commonly associated with fewer and milder complications, whereas MMC is associated with thin blebs, hypotony, and blebitis [16]. Interestingly, our study suggests that when Ologen is soaked with 5-FU intraoperatively, its IOP-lowering effect is comparable to MMC alone with the Ex-PRESS mini shunt. This may imply that the failure of Ologen, although likely multifactorial, is largely secondary to scar formation and that the addition of 5-FU may reduce this effect, resulting in improved IOP control.

In this study, complications were similar across all three groups including early and late choroidal effusion, shallow chamber, wound leak, hyphema, prolonged hypotony, and the need for re-operation. There was one endophthalmitis case in the MMC group. There is an increased risk of endophthalmitis and bleb-related infections with the addition of MMC during trabeculectomy, ranging from 2.1 to 2.6 % per patient year [5, 8, 17]. This risk is compounded by the creation of thin, avascular, or inferior blebs with thin overlying conjunctiva [4, 16, 17]. On the other hand, bleb-related infection after trabeculectomy with 5-FU is lower and has been reported at 1.7 % per year [17]. There is limited evidence on the risk of endophthalmitis with the use of Ologen, however, there was one case out of 20 patients reported in the Ologen group compared to trabeculectomy alone [11]. Our study suggests that Ologen with 5-FU could possibly replace MMC as adjunctive agent in glaucoma filtering surgery like the Ex-PRESS shunt, as it might help decrease rates of endophthalmitis while maintaining IOP. Future study of bleb morphology for the two groups will provide more information.

Our study has the limitations of a retrospective analysis. Furthermore, the sample size is small. Additionally, patients managed at a tertiary center likely represent more severe and complicated glaucoma cases, which may have influenced the rate of surgical success. Cost-effectiveness analysis was not done on any of the adjunctive agents studied here. More long-term analysis is also necessary to study IOP control and complications. A randomized-controlled trial would improve the validity of the conclusions.

In summary, we compared surgical outcome for two commonly used adjunctive agents combined with Ex-PRESS mini shunt. Ologen when used alone appears to have significantly poorer intermediate IOP control compared with standard MMC. However, Ologen with 5-FU is likely to maintain IOP as effectively as MMC. Ologen with 5-FU may help decrease severe post-operative complications, such as endophthalmitis. Future prospective studies are needed on larger groups of patients to determine if there are subgroups of patients who are better controlled or safer with MMC or with 5FU-soaked Ologen implantation as adjuncts to Ex-PRESS under a scleral flap or classical trabeculectomy.

Conflict of interest The authors declare that they have no conflict of interest and did not receive funding from any party for this research.

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